NATURE, DIAGNOSIS, AND MANAGEMENT OF NONSPECIFIC URETHRITIS*

J. DAVID ORIEL, M.D.

Director, Department of Genito-Urinary Medicine
University College Hospital
Lecturer on Venereal Diseases
University College Hospital Medical School
London, England

I N both Britain and the United States nonspecific urethritis (NSU) now is more prevalent than gonococcal urethritis. In Britain almost two thirds of the cases of urethritis reported from venereal disease (VD) clinics are nonspecific, and the number of cases has increased nearly sixfold in the last 20 years (see figure). NSU is not reportable in the United States, but there is evidence that it is common. Recent reports from two VD clinics stated that in respectively 54 and 62% of men attending with urethritis the disease was nongonococcal;[1,2] it has been estimated that in the United States NSU may constitute no less than 70% of all cases of urethritis.[3] Since many men with NSU are asymptomatic, the prevalence is probably considerably higher than published figures suggest. It is clear that NSU presents a formidable health problem.

Urethritis can be either gonococcal or nongonococcal. Nongonococcal urethritis may be due, rarely, to bacterial infection secondary to urethral trauma, foreign bodies, underlying structural disease such as stricture, or, occasionally, infection by *Trichomonas vaginalis, Candida albicans,* or *Herpesvirus simplex.* These causes are not responsible for the great majority of cases of nongonococcal urethritis, which, until recently, have been of unknown etiology; therefore, these have been designated NSU. Clinically, NSU usually presents as a low grade infection with dysuria and a scanty urethral discharge; it has been noted in VD clinics for many years.

Epidemiologic studies indicate that in many ways NSU behaves like a

---
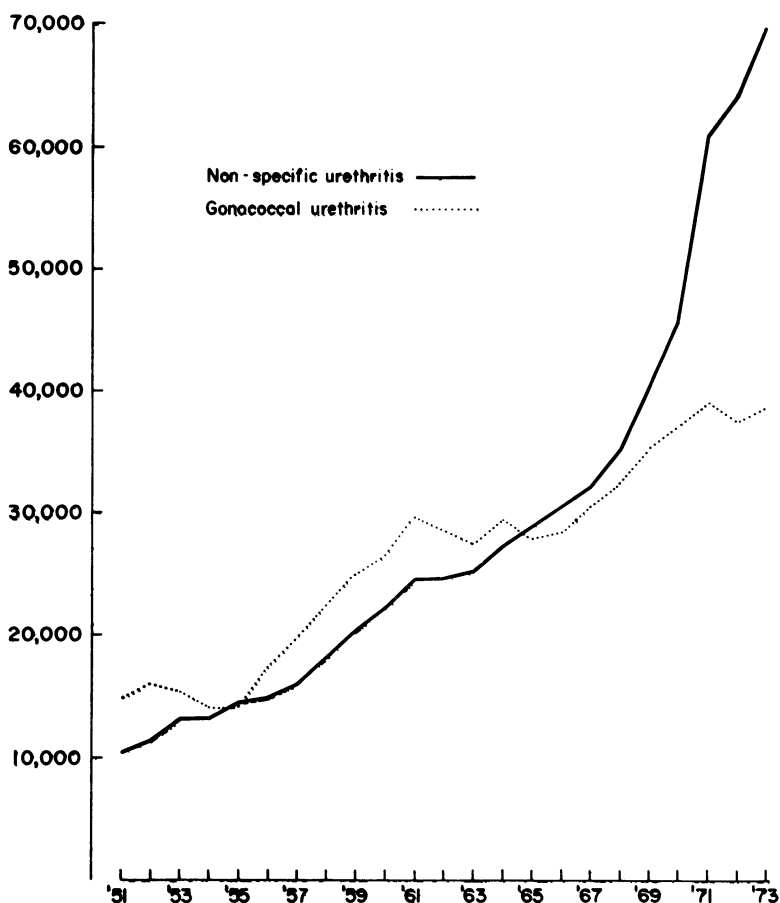
Incidence of nonspecific urethritis and gonorrhea in England and Wales, 1951 to 1973. Horizontal axis = years; vertical axis = number of cases. Courtesy Dr. R. D. Catterall.

sexually transmitted disease. In Britain gonococcal urethritis and NSU have increased side by side for more than 20 years (see figure), and show the same seasonal variation—both being commoner in the summer than in the winter.[4] Moreover, NSU usually appears after a change of sexual partner. There have been difficulties in estimating the incubation period of NSU as no "peak" time interval between exposure to infection and the onset of symptoms such as occurs in gonorrhea has been observed.[5] However, the urethral secretion in NSU may be so slight that the patient does not notice it for some time; this may account for the long incubation

MICROBIOLOGY OF 328 FEMALE CONTACTS OF MEN WITH NONSPECIFIC
URETHRITIS. UNIVERSITY COLLEGE HOSPITAL, LONDON

Organisms isolated	No. of patients	Percentage of total
Chlamydia trachomatis	73	22
Neisseria gonorrhoeae	16	5
Trichomonas vaginalis	11	3
Candida albicans	32	10
Mixed infections	21	6
No pathogens isolated	175	53

periods which are sometimes described.[6] In the majority of patients, the incubation period of NSU appears to be between one and three weeks.[7]

In recent years much research has been directed toward identifying the causal agent or agents of NSU; rational therapy and control of NSU through the identification of infected women will be nearly impossible until this has been achieved. It is now believed that infection by *Chlamydia trachomatis* is the cause of a substantial number of cases. Although inclusions, now known to be chlamydial, were identified in urethal scrapings from some men with NSU more than 50 years ago, the association with *C. trachomatis* could not be adequately studied until a sensitive cell-culture system was devised by Gordon and Quan in 1965.[8] Using cell-culture procedures, groups of workers in both Britain and the United States within the last few years have reported the recovery of *C. trachomatis* from urethral specimens in between 40% and 60% of men with NSU;[2,9,10-12] the isolation rate depends upon the technique of collecting specimens, the sensitivity of the cell-culture system used, and the duration of the patients' symptoms when specimens were obtained. Seroconversion and the presence of IgM antibodies to *C. trachomatis* have been demonstrated by immunofluorescence in some men with NSU from whom the organism was isolated.[2,13] Groups of men without urethritis, comparable in sexual activity to the men with NSU, yield *C. trachomatis* in 7% or less of cases.[2,7] Finally, epidemiologic studies have shown that more than 80% of the female contacts of men with *Chlamydia*-positive NSU have a demonstrable chlamydial infection of the cervix.[14] The etiologic role of *C. trachomatis* in NSU thus appears to be secure.

There are also many men with NSU from whom *C. trachomatis* has not

been recovered, and the cause of the disease in these cases is uncertain. It is possible that refinements in techniques of isolation may lead to the recovery of the organism from some patients who are isolation-negative with present methods, but it is unlikely that *C. trachomatis* is the only cause of NSU. Other etiologic agents must be sought. For many years it was thought that T-mycoplasmas might be an important cause, as they were recovered from more than 70% of patients with NSU.[15] However, control groups of men without urethritis matched in sexual behavior with the NSU groups were found to yield T-mycoplasmas with similar frequency,[2,16] and it is now thought that the organisms are not a major cause of NSU, although the possibility that they may cause a few cases has not been excluded. There is no evidence that *M. hominis, C. vaginale,* or other aerobic bacteria cause any cases; the possibility that anaerobic bacteria may be causal agents has been suggested[17] and awaits further study. *T. vaginalis* infestation can cause urethritis in men, but there is no evidence that it is of major importance in the etiology of NSU.[2]

The clinical features of NSU are familiar. The patient usually complains of urethral irritation (a characterisitic symptom), dysuria, or urethral discharge, although some men with NSU are asymptomatic.[18] Examination reveals a variable degree of hyperemia of the terminal urethra and a scanty mucoid or mucopurulent discharge or, indeed, no discharge if the patient has recently passed urine. The relatively mild symptoms may lead patients to defer seeking medical advice, in contrast to men with gonorrhea, who usually seek aid within a few days of the onset.[1]

The diagnosis of NSU depends on the demonstration of a significant degree of urethritis and the exclusion of *N. gonorrheae* and other likely causes. NSU and gonorrhea cannot be differentiated clinically with uniform accuracy. Although the urethritis of NSU is usually mild, it is sometimes severe, with a profuse discharge and, conversely, gonorrhea may be mild or even asymptomatic.[19] Therefore, in all cases of urethritis gonorrhea must be excluded. The traditional Gram-stained urethral smear is simple, rapid, and at least 90% accurate. However, since both false-positive and false-negative results occur,[20] microscopy should be supplemented by culture in all cases. In addition to tests for *N. gonorrheae,* some physicians also perform microscopy of a urethral specimen suspended in saline to exclude trichomonal infestation.

The demonstration of significant urethritis is of particular importance in making the diagnosis of NSU, where subclinical infections are not un-

usual. Two methods are in use. In the first, polymorphonuclear leukocytes are enumerated in the Gram-stained urethral smear, more than 10 per mean of three fields at magnification of 900 being considered significant. A two-glass test of urine is then performed, any threads being examined similarly. In the second method the first 10 ml. of urine passed is centrifuged, the deposit resuspended, and microscopy performed. Pyuria, indicating significant urethritis, is defined as the presence of more than 20 leukocytes in at least one of five fields examined with a magnification of 400.[2] There is probably little difference between the results of these two techniques. However, in both the results must be related to the time when the patient last passed urine; negative results do not exclude significant urethritis unless three hours or more have elapsed. If necessary, the patient should be asked to return for re-examination after he has held urine for at least three hours or, preferably, overnight.

The diagnosis of NSU, thus, can be made by simple means: microscopy of urethral material, urethral culture for *N. gonorrheae*, and examination of the urine. How should it be treated? It sometimes is suggested that NSU is a mild and self-limiting disease and that treatment is unnecessary. This view is totally mistaken. Failure to treat NSU adequately subjects the patient to discomfort, anxiety, and the possibility of later complications such as prostatitis or even urethral stricture. In addition, it increases the risk of spread of the infection to others. Satisfactory therapy is as necessary for NSU as it is for gonorrhea.

The clinical requirements for treating any infectious disease are 1) elimination of the causal agent, 2) the abolition of the symptoms and signs of the disease, and 3) a regime which is preferably simple and rapidly effective. In the case of sexually transmitted diseases, a fourth requirement should be added: the identification and treatment of infected sexual contacts. All these requirements are, to a large extent, fulfilled in the therapy of gonorrhea. In the case of NSU the situation has been less satisfactory, chiefly because of our lack of knowledge of the cause of the disease. A great variety of therapies for NSU are in use, a state of affairs which contrasts sadly with the general agreement on the basic principals of treating gonorrhea.

The management of NSU involves the patient himself and his sexual contacts. For the patient, antimicrobial therapy is indicated. Holmes and his colleagues[21] were the first investigators to show conclusively in a double-blind trial that tetracycline was superior to a placebo. It has been

known for many years that NSU does not respond to penicillin or ampicillin, although both, unfortunately, still are prescribed widely. With tetracycline or oxytetracycline, the effective dosage is 1 to 2 gm. daily, given in divided doses. Minocycline, 100 mg. twice daily, is also effective, and for patients who are unable to take tetracycline, erythromycin, 250 mg. every six hours, is a satisfactory alternative.

There appear to be advantages in prolonging the course of therapy beyond the stage of initial clinical improvement, and many workers feel that the customary five or seven day courses are too short. Courses of tetracycline therapy of two or even three weeks' duration have been recommended as reducing the patient's tendency to relapse.[22] It is of interest that tetracyclines are known to be active *in vitro* against *C. trachomatis*.[23] In a recent investigation[24] it has been shown that minocycline, when given in a three-week course, is uniformly effective in eliminating *C. trachomatis* from the urethra of men with *Chlamydia*-positive NSU, this being accompanied in the majority of patients by the disappearance of the clinical signs of infection.

On present evidence, tetracyclines such as oxytetracycline, tetracycline, or minocycline are the best antibiotics to use in the therapy of NSU and should be given in courses of not less than two weeks' duration. During this period the patient should refrain from sexual intercourse and reduce his consumption of alcohol. After therapy patients will require follow-up for at least four weeks. The initial diagnostic tests are repeated to confirm that the patient no longer has significant urethritis. If he is symptom-free and these tests are negative on two or three occasions after therapy has been completed, he may be regarded as clinically cured. The possible benefits to the patient of more prolonged follow-up must be weighed against the possibility that too frequent attendance and examination may render him anxious and introspective. Whether examination of the prostatic fluid should form part of the routine follow-up is a matter of opinion. It is recommended by some physicians, but others feel that the examination contributes little information of clinical value.

At best, such treatment regimes will cure about 80% of men with NSU. The remainder will continue to have symptoms and signs of urethritis, and some others will relapse subsequently after intercourse is resumed. Many of these relapses are in reality reinfections, particularly if the patient's sexual contacts have not been adequately treated. However, it is possible that in some patients therapy, in fact, will not eliminate the causal agent;

in such cases the urethritis still may be present after antibiotic treatment or it may reappear after an interval during which there have been no symptoms. Longer courses of therapy or the administration of a different antibiotic may be required for these patients. Some light may be thrown on the problem of recurrent NSU by prospective studies—particularly of men who yield isolates of *C. trachomatis*—which are at present in progress.

No sexually transmitted disease affecting men can be managed clinically or controlled epidemiologically unless infected female contacts are located and treated. This policy is pursued vigorously for men with gonococcal urethritis; it is surprising that similar efforts are not usually made in the case of men with NSU. Data from University College Hospital in London (see table) showed nearly 50% of a group of 328 female contacts of men with NSU to have one or more genital pathogens, of which the commonest was *C. trachomatis*. The value of investigating these women is apparent; in addition, in this group a small number of unforeseen gonococcal and trichomonal infections requiring specific therapy were found. It is not possible to make a clinical diagnosis of nonspecific genital infection in women. Female contacts of men with NSU, even those with a demonstrable chlamydial infection, do not show any distinctive clinical abnormalities on routine examination; for this reason it is recommended that a full course of tetracycline therapy be given to all such contacts. There must be many other women with nonspecific genital infections in whom the diagnosis is not made or even suspected in the absence of a history of contact with an infected man. The identification and treatment of these women is of the utmost importance; how this is to be done awaits the progress of current research.

In many ways NSU has been a stepchild in the family of sexually transmitted diseases. For years, the more lurid manifestations of gonococcal urethritis led many physicians to ignore NSU, and even today it is sometimes regarded as a minor problem of little importance. This is untrue. NSU is an increasingly common disease which patients find worrisome and unpleasant. It is liable to complications—epididymo-orchitis, prostatitis, and urethral stricture in men and salpingitis in their female contacts. Babies born to women with nonspecific genital infections are likely to develop neonatal eye infections; if these are chlamydial they are potentially serious without proper treatment. Finally, there is an unexplained association between NSU and Reiter's disease. When considered in terms of prevalence, liability to complications, lack of knowledge

on etiology, and uncertainty about effective treatment, NSU is the biggest problem in present-day venereology.

SUMMARY

NSU now is probably the most prevalent sexually transmitted disease in Britain and the United States. The causal agent is believed to be *Chlamydia trachomatis* in 50 to 60% of cases, but the cause of the remainder is unknown. The clinical features and the methods used for the diagnosis of NSU have been described. The necessity of adequate treatment has been emphasized; tetracyclines are the antimicrobial agents of first choice, and some recommended treatment schedules have been described. The importance of investigating and treating female contacts of men with NSU was stressed.

REFERENCES

1. Jacobs, N. F. and Kraus, S. J.: Gonococcal and nongonococcal urethritis in men. *Ann. Intern. Med. 82:*7, 1975.
2. Holmes, K. K., Handsfield, H. H., Wang, S. P., Wentworth, B. B., Turck, M., Anderson, J. B., and Alexander, E. R.: Etiology of non-gonococcal urethritis. *New Eng. J. Med. 292:*1199, 1975.
3. Kaufman, R. E. and Wiesner, P. J.: Current concepts: Non-specific urethritis. *New Eng. J. Med. 291:*1175, 1974.
4. Csonka, G. W.: Non-gonococcal urethritis. *Brit. J. Vener. Dis. 41:*1, 1965.
5. Boyd, J. T., Csonka, G. W., and Oates, J. K.: Epidemiology of non-specific urethritis. *Brit. J. Vener. Dis. 34:*40, 1958.
6. King, A.: *Recent Advances in Venereology.* London, Churchill, 1964, p. 353.
7. Oriel, J. D., Reeve, P., Powis, P., Miller, A., and Nicol, C. S.: Chlamydial infection. Isolation of chlamydia from patients with non-specific genital infection. *Brit. J. Vener. Dis. 48:*429, 1972.
8. Gordon, F. B. and Quan, A. L.: Isolation of the trachoma agent in cell culture. *Proc. Soc. Exp. Biol. Med. 118:*354, 1965.
9. Dunlop, E. M. C., Vaughan-Jackson, J.

D., Darougar, S., and Jones, B. R.: Chlamydial infection. Incidence in "non-specific" urethritis. *Brit. J. Vener. Dis. 48:*425, 1972.
10. Richmond, S. J., Hilton, A. L., and Clarke, S. K. R.: Chlamydial infection. Role of Chlamydia subgroup A in non-gonococcal and post-gonococcal urethritis. *Brit. J. Vener. Dis. 48:*437, 1972.
11. Schacter, J., Hanna, L., Hill, E. C., Massad, S., Shepard, C. W., Conte, J. E., Cohen, S. N., and Meyer, K. F.: Are chlamydial infections the most prevalent venereal disease? *J.A.M.A. 231:*1252, 1975.
12. Oriel, J. D., Reeve, P., Wright, J. T., and Owen, J.: Chlamydial infection of the male urethra. *Brit. J. Vener. Dis. 52:*46, 1976.
13. Reeve, P., Gerloff, R. K., Casper, E., Philip, R. N., Oriel, J. D., and Powis, P. A.: Serological studies on the role of *Chlamydia* in the aetiology of non-specific urethritis. *Brit. J. Vener. Dis. 50:*136, 1974.
14. Oriel, J. D., Reeve, P., Wright, J.T., and Owen, J.: Epidemiology of chlamydial genital infection. In preparation.
15. Shepard, M. C.: Nongonococcal urethritis associated with human strains of "T"

mycoplasmas. *J.A.M.A. 211:*1335, 1970.

16. McCormack, W. M., Lee, Y. H., and Zinner, S. H.: Sexual experience and urethral colonisation with genital mycoplasma. A study in normal men. *Ann. Intern. Med. 78:*696, 1973.

17. Hafiz, S., McEntegart, M. G., Morton, R. S., and Waitkins, S. A.: *Clostridium difficile* in the urogenital tract of males and females. *Lancet 1:*420, 1975.

18. Rodin, P.: Asymptomatic non-specific urethritis. *Brit. J. Vener. Dis. 47:*452, 1971.

19. Portnoy, J., Mendelson, J., Clecner, B., and Heisler, L.: Asymptomatic gonorrhoea in the male. *Canad. Med. Ass. J. 110:*169, 1974.

20. Philips, I., Humphrey, D., Middleton, A., and Nicol, C. S.: Diagnosis of gonorrhoea by culture on a selective medium containing vancomycin, colistin, nystatin and trimethoprim. *Brit. J. Vener. Dis. 48:*287, 1972.

21. Holmes, K. K., Johnson, D. W., and Floyd, T. M.: Studies of venereal disease. III. Double-blind comparison of tetracycline hydrochloride and placebo in treatment of non-gonococcal urethritis. *J.A.M.A. 202:*474, 1967.

22. John, J.: Efficacy of prolonged regimes of oxytetracycline in the treatment of non-gonococcal urethritis. *Brit. J. Vener. Dis. 47:*266, 1971.

23. Jawetz, E.: Chemotherapy of chlamydial infections. *Advances Pharmacol. Chemother. 7:*253, 1969.

24. Oriel, J. D., Reeve, P., and Nicol, C. S.: Minocycline in the treatment of non-gonococcal urethritis—its effect on *Chlamydia trachomatis. J. Amer. Vener. Dis. Ass. 2:*17, 1975.